UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/516,754	02/08/2006	Christopher Frederickson	NBT-000200US	6895

68514 7590 12/27/2010

Don D. Cha
225 Union Blvd
Suite 150
Lakewood, CO 80228

EXAMINER	
SCHLIENTZ, LEAH H	

ART UNIT	PAPER NUMBER
1618	

NOTIFICATION DATE	DELIVERY MODE
12/27/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

DCHA@HDCIPLAW.COM
DDCha@Comcast.net
Joshua@HDCIPLaw.com

Office Action Summary	Application No.	Applicant(s)	
	10/516,754	FREDERICKSON ET AL.	
	Examiner	Art Unit	
	Leah Schlientz	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 July 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *37-66* is/are pending in the application.

4a) Of the above claim(s) *44 and 45* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *37-43 and 46-66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12/3/2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Acknowledgement of Receipt

Applicant's Response, filed 7/26/2010, in reply to the Office Action mailed 10/28/2009, is acknowledged and has been entered. Claims 1-36 have been cancelled. Claims 37-66 are newly added. Claims 37-66 are pending, of which claims 44 and 45 are withdrawn from consideration at this time as being drawn to a non-elected invention. Claims 37-43 and 46-66 are readable upon the elected invention and are examined herein on the merits for patentability.

Response to Arguments

Applicant's arguments have been fully considered, but are moot in view of new grounds of rejection, set forth in view of newly discovered prior art references.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 37 is rejected under 35 U.S.C. 102(b) as being anticipated by Krongrad (US 5,250,284).

Krongrad discloses that methods for detection, spectra analysis and imaging the concentration and characteristics of magnetic nuclei in living biological tissue. Magnetic isotopes are administered to living biological tissue in a chemical form in which it is bioavailable and at concentration levels greater than naturally occurring concentration levels, i.e. at which the magnetic isotope has been enriched. The magnetic isotope administered is selected from isotopes of elements which are metabolized by the living biological tissue. The tissue is allowed to absorb and metabolize the isotope. The tissue is then, for example, subjected to a magnetic field which will orient all nuclei with nonzero spin and generate a net magnetic moment M, aligned parallel to the field, within the tissue. When the excitation magnetic pulse is interrupted, the nuclei return to their original equilibrium with characteristic resonance. In the process the nuclei emit radiation in the radio frequency region of the electromagnetic spectrum. This radiation is detected and converted into spectra or images which reflect the concentration and chemical characteristics of the nuclei. These spectra or images are then used to study the normal physiology of the isotope and following this to detect abnormal biology (column 3, line 55 – column 4, line 11). Examples of the general application of this method include the study of cancer or other diseases in animals including humans. Examples of the specific application of the present method include the study of prostate or the pancreas using ^{67}Zn which has a low natural abundance of about 4%. However Zn plays an important role for the function of each of these glands. Cancerous conditions as well as other abnormalities may be detected, or more accurately staged at early stages of the cancer or other disease (column 6, lines 1-9). Specifically,

nonradioactive magnetic isotope ^{67}Zn in increased concentrations (i.e. greater than 4% natural abundance level) is administered to a patient with recently diagnosed prostate cancer. Before, during and/or after administration, the patient undergoes MRI utilizing probes configured to measure the ^{67}Zn resonance. Following conversion to anatomical images, determinations of focal altered zinc concentrations are made, with confirmation of pathology by aspiration cytology or biopsy (Example 1). See also claims 1-15.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 37-43, 46-52, 54-63, 65 and 66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Krongrad (US 5,250,284) in view of Meade (US 5,707,605), in further view of Song (*Am. J. Physiol. Cell Physiol.*, 1995, 269, C318-C322) and Csermely (*Biochem. Biophys. Res. Commun.*, 1989, 165(2), p. 838-844 (abstract)).

Krongrad discloses that methods for detection, spectra analysis and imaging the concentration and characteristics of magnetic nuclei in living biological tissue. Magnetic isotopes are administered to living biological tissue in a chemical form in which it is bioavailable and at concentration levels greater than naturally occurring concentration levels, i.e. at which the magnetic isotope has been enriched. The magnetic isotope administered is selected from isotopes of elements which are metabolized by the living biological tissue. The tissue is allowed to absorb and metabolize the isotope. The tissue is then, for example, subjected to a magnetic field which will orient all nuclei with nonzero spin and generate a net magnetic moment M, aligned parallel to the field, within the tissue. When the excitation magnetic pulse is interrupted, the nuclei return to their original equilibrium with characteristic resonance. In the process the nuclei emit radiation in the radio frequency region of the electromagnetic spectrum. This radiation is detected and converted into spectra or images which reflect the concentration and chemical characteristics of the nuclei. These spectra or images are then used to study the normal physiology of the isotope and following this to detect abnormal biology (column 3, line 55 – column 4, line 11). Examples of the general application of this method include the study of cancer or other diseases in animals including humans. Examples of the specific application of the present method include the study of prostate or the pancreas using .sup.67 Zn which has a low natural abundance of about 4%. However Zn plays an important role for the function of each of these glands. Cancerous conditions as well as other abnormalities may be detected, or more accurately staged at early stages of the cancer or other disease (column 6, lines 1-9). Specifically,

nonradioactive magnetic isotope ^{67}Zn in increased concentrations (i.e. greater than 4% natural abundance level) is administered .to a patient with recently diagnosed prostate cancer. Before, during and/or after administration, the patient undergoes MRI utilizing probes configured to measure the ^{67}Zn resonance. Following conversion to anatomical images, determinations of focal altered zinc concentrations are made, with confirmation of pathology by aspiration cytology or biopsy (Example 1). See also claims 1-15.

Accordingly, Krongrad teaches MRI imaging of zinc concentration as a means of determining prostate health, but does not recite using a zinc complexing agent such as F-BAPTA for ^{19}F MRI imaging of zinc ion concentration. However, one skilled in the art would be aware of other imaging techniques available for assessing zinc ion concentration, such as use of a zinc binding agent for ^{19}F MRI.

Meade teaches magnetic resonance imaging agents comprising a paramagnetic metal ion bound to a complex wherein said complex comprises a chelator and a blocking moiety covalently attached to said chelator which binds in at least a first coordination site of said metal ion and which is capable of interacting with a target substance such that the exchange of water in at least said first coordination site is increased (abstract). A blocking moiety may be a calcium binding substance such as known in the art (such as BAPTA), and the target substance may be Ca^{2+}, Mg^{2+}, Zn^{2+}, Na^{+}. The metabolite may be associated with a particular disease or condition within an animal. For example, BAPTA-DOTA derivatives may be used to diagnose Alzheimer's disease or other neurological disorder (column 16, lines 26+; column 20, column 25, lines 45+). Targeting agents are also disclosed (column 23). Functional MRI contrast

agents may be used to perform rapid screens of the physiological response to drug therapy (column 25, lines 6-7).

Song teaches measurement of intracellular calcium concentration in vivo and in situ using ^{19}F-NMR and 5f-BAPTA (page C318, right column). Experiments were performed on rats with surface coil antenna employed for NMR interrogation. The Ca^{2+} indicator, 5F-BAPTA, was infused either intravenously (kidney, spleen) or intraventricularly (brain) as a 100 mg/ml solution of the cell-permeant acetoxy methyl ester (5F-BAPTA-AM) in dimethyl sulfoxide. In all tissues examined, kidney, spleen, and brain $[Ca^{2+}]_i$, was 200 nM (abstract). NMR acquisition parameters are detailed on page C319. See also Figures disclosed page C320 depicting 19F NMR spectra and $[Ca^{2+}]_i$ concentration derived therefrom. Although both kidney and spleen were exposed by surgical incision to place the surface coil in close proximity to the organ and thus maximize signal-to-noise ratio (allowing 5 to 10 min. time resolution), surgical exposure of organs can be avoided using magnetic resonance imagery-related single volume localization techniques (page C322, left column).

Csermely teaches that increasing interest is focused on the role of zinc in biological systems. A rapidly growing family of DNA-binding proteins contains “zinc-fingers”, where zinc is bound to cysteine or histidine residues. On the other hand zinc is able to displace calcium from its binding sites and in this way it may modify calcium-mediated cellular processes. In the present report dissociation rates of Zn^{2+} and Ca^{2+} complexes with 5-F-BAPTA, a widely used NMR-active calcium indicator, have been measured by two-dimensional ^{19}F NMR exchange spectroscopic methods. The results

show that the lifetime of the Zn^{2+} complex is more than five times longer than that of the Ca^{2+} complex. The longer lifetime, when combined with a higher thermodynamical stability of the Zn^{2+} complex, may explain why, in some cellular processes, Zn^{2+} can compete with Ca^{2+} in spite of a presumably high $[Ca^{2+}]/[Zn^{2+}]$ free ion concentration ratio (abstract).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Krongrad, Meade, Song and Csermely in order to achieve prostate cancer determination based upon ^{19}F MRI imaging of zinc ion concentration using a known zinc complexing agent such as F-BAPTA. While Krongrad teaches MRI imaging of prostate cancer using enriched ^{67}Zn, one of ordinary skill would have recognized that use of metal binding ion complexing agents (e.g. BAPTA known to complex Zn^{2+} and Ca^{2+}) as a suitable and predictable potential solution to imaging of metal ion concentration, as shown by Meade and Song using DOTA-BAPTA or F-BAPTA and imaging by ^{1}H or ^{19}F MRI, respectively. One would have had a reasonable expectation of success in imaging zinc ion bound by F-BAPTA using ^{19}F MRI as equivalent to calcium because Csermely teaches that increasing interest is focused on the role of zinc in biological system and because Zn^{2+} shows longer lifetime and higher thermodynamic stability than Ca^{2+} when complexed with F-BAPTA as shown by ^{19}F NMR. With respect to the limitation of claim 38 regarding “acquiring imaging signals via at least one imaging scan of said non-hydrogen imaging nucleus, generating at least one image map comprising intensity of an image pixel derived from said imaging signal..., and correlating intensity of said image pixel at any point on said image map or

on a subtractive composite of said image maps with concentration of said zinc ion in the prostate at said mapping point," it is noted that Krongard teaches conversion of imaging signal to anatomical images and determinations of focal altered zinc concentrations. With regard to the limitations of claims 39 and 48-52, it is noted that complexing agent selectivity and relaxation times would be an inherent feature of a given complexing agent. Regarding the claimed functional properties, the Office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same functional characteristics of the claimed product. In the absence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See *Ex parte Phillips*, 28 U.S.P.Q.2d 1302, 1303 (PTO Bd. Pat. App. & Int. 1993), *Ex parte Gray*, 10 USPQ2d 1922, 1923 (PTO Bd. Pat. App. & Int.) and *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977). In the instant case, Csermely teaches ^{19}F NMR of zinc using F-BAPTA. Since F-BAPTA is the same contrast agent as that which is claimed, it is interpreted, absent evidence to the contrary, that the agent would be capable of achieving the claimed selectivity and relaxation properties. Regarding claims 55 and 65, Meade teaches that MRI is known in the art for monitoring physiologic response to a drug.

Claims 37-43 and 46-66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Krongrad (US 5,250,284) in view of Meade (US 5,707,605), in further

view of Song (*Am. J. Physiol. Cell Physiol.*, 1995, 269, C318-C322), Csermely (*Biochem. Biophys. Res. Commun.*, 1989, 165(2), p. 838-844 (abstract)) and Mason (*Magn. Res. Imaging*, 1989, 7(5), p. 475-85 (abstract)).

The rejection over Krongrad in view of Mead, in further view of Song and Csermely is applied as above. Krongrad, Mead, Song and Csermely do not specifically recite a spin-echo imaging scan as required by claims 53 and 63.

Mason teaches multiresonance perfluorocarbon emulsions (Oxypherol and Fluosol-DA) were imaged in tumor-bearing mice using ^{19}F spin-echo magnetic resonance imaging in vivo. Multiple thin-slice fluorine images free of chemical shift artifacts were obtained in 13 minutes and these were correlated with proton images obtained during the same experiment to delineate the anatomic distribution of perfluorocarbons. Sequential images were used to determine the time course of the distribution and the retention of the compounds in tumors and organs. ^{19}F MR spectroscopy was used ex vivo to determine with high sensitivity the relative concentration of perfluorocarbons in different tissues and organs and to confirm the results obtained from imaging experiments. The fluorine images visually demonstrated the preferential localization of the perfluorocarbons in the liver and spleen; shortly after injection, the images also revealed the highly vascularized tumor/chest wall interface. Imaging and spectroscopy together showed that the perfluorocarbons were removed from the blood pool within hours and remained sequestered in tissues at later times; the highest concentrations were found in the spleen and liver, where the agents were retained without spectral changes for the duration of these studies. The

perfluorocarbons accumulated within tumors at dose-dependent concentration, one to two orders of magnitude smaller than those observed in the spleen and liver (abstract).

It would have been obvious to one of ordinary skill in the art to employ a spin-echo imaging scan as means of obtaining ^{19}F MRI imaging of zinc concentration in prostate when the teachings of Krongrad, Mead, Song and Csermely are taken in view of Mason. Krongrad teaches desirability of an anatomical map of zinc ion concentration for imaging prostate cancer. One would have had a reasonable expectation of success in using ^{19}F spin-echo scan magnetic resonance imaging for generating an map of zinc ion concentration using F-BAPTA for complexing zinc because Mason shows that ^{19}F spin echo scanning can be used to delineate concentration/anatomic distribution of contrast agent in vivo, albeit with a different ^{19}F marker.

Conclusion

No claims are allowed at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leah Schlientz whose telephone number is (571)272-9928. The examiner can normally be reached on Monday-Tuesday and Thursday-Friday 9 AM-5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618

LHS